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preclinical breast cancer biology

90P Dual role of endothelial cell signaling in cancer progression

D.A. Ferraro[1], R. Goosen[1], F. Patella[2], S. Zanivan[2], M. Buess[1], G. Christofori[1]
[1]*Department of Biomedicine, University of Basel, Basel, Switzerland*
[2]*Vascular Proteomic Laboratory, University of Glasgow Beatson Institute for Cancer Research, Glasgow, UK*

The microenvironment is known to be a central regulator of tumor biology. While the contribution of fibroblasts and macrophages has been largely studied, the role of endothelial cells as regulators of cancer cell behavior is still poorly understood. As in a diverse spectrum of pathophysiological processes in normal tissue, endothelial cells may exert a similar regulatory control in malignant cancer progression and metastasis, not only contributing to vessels formation, but also through endothelial cell specific signals. To characterize the role of stromal endothelial cells, we first analyzed endothelial paracrine signaling and its effect on breast cancer cells. SKBR3 cells treated with HUVEC derived supernatant show significantly increased migratory potential, without a parallel increase in proliferation, an elongated phenotype and expression of mesenchymal markers (up-regulation of FN1, Stress Fibers and Focal Adhesion formation). The pro-migratory effect is significantly more pronounced when the supernatant is obtained from a sparse and highly proliferative endothelial culture than from confluent and resting endothelial cells. To better investigate the differential regulation on cancer cells migration, we analyzed the supernatant of sparse or dense endothelial cells by quantitative MS proteomics (SILAC analysis). Interestingly, extracellular matrix proteins were found enriched in dense endothelium supernatant. Amongst them, Biglycan reduced the pro-migratory effect of treatment with sparse endothelium supernatant, suggesting a potential role of resting endothelium as an inhibitor of cancer cell migration. The proteomic analysis of sparse endothelial cell supernatant revealed the enrichment in proteins belonging to the micro-vesicular compartment. Knocking down these proteins significantly reduced the pro-migratory effect of the endothelial supernatant on cancer cells, demonstrating that the vesicular compartment can play a role in the modulation of tumor aggressiveness. We suggest that identification of endothelial cell role in microenvironment induced cancer progression could reveal new targets for novel therapeutic strategy.

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